REMARKS

Reconsideration is requested.

Claims 1-19 are pending. Claims 7, 11-14, 17 and 18 have been withdrawn from consideration.

The Section 103 rejection of claims 1-6, 8-10, 15, 16 and 19 over Chauvierre (WO 02/39979) and Desai (U.S. Patent No. 6,096,331), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

The applicants submit, with due respect, that Desai does not teach that a biocompatible agent, which is hemoglobin, may be associated with the nanoparticle shell comprising a polysaccharide so as to be useful as a blood substitute. Consideration of the following in this regard is requested.

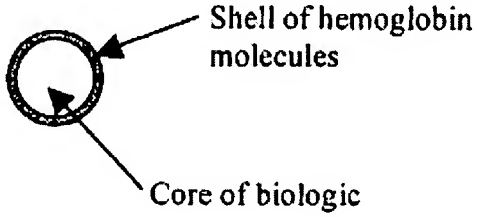
The applicants believe that the only section in the entire Desai patent dealing with a hemoglobin particle for use as a blood substitute is found in the following from column 11, lines 60-67:

> "In some cases, the biocompatible material forming the shell about the core could itself be a therapeutic or diagnostic agent, e.g., in the case of insulin, which may be delivered as part of a polymeric shell formed in the process described above. In other cases, the polymer forming the shell could participate in the delivery of a biologic, e.g., in the case of antibodies used for targeting, or in the case of hemoglobin, **which may be delivered as part of a polymeric shell formed in the ultrasonic irradiation process described above**, thereby providing a blood substitute having a high binding capacity for oxygen.

The only description of an ultrasonic irradiation process in the patent can be found in Examples 1 and 3, which is understood to describe the formation of an

albumin microemulsion (i.e., a colloidal solution of particles whose shell is made of albumin molecules).

Thus, the "blood substitute" that Desai is referring to is a nanocapsule in which the hemoglobin molecules form the shell.



Desai does not suggest, much less teach, the association of hemoglobin on a nanoparticle shell comprising a polysaccharide for purposes of making a blood substitute. The Examiner is believed to be picking and choosing aspects of the cited art without examining the references in their entirety. The Examiner's interpretation and application of the cited art is submitted to in hindsight, as opposed to what one of ordinary skill would have expected from the cited art in the absence of the applicants disclosure.

Since neither the Chauvierre nor the Desai teaches or suggests the association of hemoglobin with a polysaccharide-coated nanoparticle for use as a blood substitute, the cited combination of references cannot support a prima facie case of obviousness.

Further, the applicants believe that Desai is not enabling for making and/or using "hemoglobin shells". Specifically, Desai is understood to include the statement that his "hemoglobin shells" can function as a blood substitute without enabling the ordinarily skilled artisan to practice this aspect of Desai's disclosure. In particular, Desai provides

no teaching or working example of how this might be accomplished, nor any confirmatory tests establishing that the hemoglobin comprising the shell of the microcapsule has the ligand binding/releasing capability that is required to achieve its function as a blood substitute. There are other parameters that Desai may have confirmed before asserting that his hemoglobin particles provided "a blood substitute having a high binding capacity for oxygen" or were suitable for therapeutic administration. It is noted in this regard that Desai fails to demonstrate the products did not provoke an antigenic reaction, that they had a sufficient blood circulation life, that they could bind and release oxygen, that little oxidation of the hemoglobin iron took place and that the hemoglobin retained its allosteric function.

Desai provided no proof in support of his statement, not even experimental data demonstrating the most fundamental property: that hemoglobin's ability to bind and release ligands is preserved.

The applicants further note that there is no reasonable expectation of success from the cited combination of art that the claimed invention could be made and/or used.

The Examiner asserts that the reasonable expectation of success criteria is met because the artisan allegedly needs to only follow the teachings of Desai to add hemoglobin to the nanoparticle of Chauvierre to create the instantly claimed composition. The Examiner is understood to believe that there is reasonable expectation of successfully producing the claimed invention from the cited art because of an alleged well established recognition that heparin, being polyanionic in nature, has a high affinity for basic proteins like hemoglobin.

First, as discussed above, Desai does not teach the association of hemoglobin to a particle comprising a polysaccharide shell. Therefore, someone following Desai's teaching could not have achieved the presently claimed subject matter. In fact, someone looking to achieve the presently claimed particles would not identify Desai as a relevant reference, nor would they look to Desai's teachings.

Secondly, even if the Desai and Chauvierre references could hypothetically have been combined to make the claimed particles, the test of reasonable expectation of success is not whether hemoglobin could associate with the nanoparticles taught in the Chauvierre et al. reference, but whether the resulting particles would have the claimed utility (t e., that they can function as blood substitute).

One cannot deduce from merely reading the cited references that hemoglobin associated with the oligosaccharide or polysaccharide hydrophilic segment coating the particle, as claimed, would retain a reversible ligand-binding capacity, which is a property that is essential for its gas-transporter role (i.e., property that is critical for the particle to be suitable for use as blood substitute or depolluting agent).

This property cannot be predicted nor ascertained without first conducting experiments.

For example, as discussed in the cited Chauvierre et at reference, it is known that the surface properties of core-shell nanoparticles prepared from amphiphilic copolymers such as those described in the Chauvierre et at reference, can vary greatly depending on the polymerization method. As taught by Chauvierre et al, anionic polymerization of an alkylcyanoacrylate in presence of a polysaccharide such as dextran leads to branched copolymers that self associate into nanoparticles that are

rapidly taken up by the niacrophages of the Mononuclear Phagocyte System (MPS). Their lifetime in vivo is therefore reduced. In contrast, when free radical polymerization is used, sequenced copolymers are obtained that associate into nanoparticles where the polysaccharide chains are arranged as a brush at the nanoparticle surface. It is this "brush-like" structure that confers to the nanoparticles the long circulating life that is essential for their application as blood substitute, There was no reasonable expectation of success from the cited references, or from the general knowledge in the art, that the surface properties of the nanoparticles, in particular their long- circulating life in blood, would not be negatively impacted if they were associated with hemoglobin. The inventors demonstrated that it was the case. (Chauvierre et at, Cell. Molec. Biol., 2004, 50(3), 233-239).

Similarly, there was no reasonable expectation of success that the hydrodynamic radius of these nanoparticules would not be negatively affected by association of hemoglobin at their surface. The inventors demonstrated that the size of heparin coated nanoparticles was not significantly affected by the association of hemoglobin (Chauvierre et al, Cell. Molec. Biol., 2004, 50(3). 233-239; Chauvierre et al, Biomaterials, 2004, 25, 3081-3086).

Finally, there was no reasonable expectation of success that the associated hemoglobin would retain its capacity of transporting gases such as oxygen or carbon monoxide. Again, the inventors demonstrated that hemoglobin was functional. (Chauvierre et al, Cell. Molec. Biol., 2004, 50(3), 233-239).

It is also important to note that the quantities of hemoglobin associated at the surface of the nanoparticle may vary greatly depending on the nature of the

polysaccharide present at the surface of the nanoparticle andlor depending on whether the copolymer is branched ("loop like" structure) or sequenced ("brush-like" structure). The following examples illustrate this principle:

	Polysaccharide	Nanoparticle type and structure	Hemoglobin loading capacity (mg/ml)
1	Dextran (70 kDa)	PIBCA – "loop-like" structure"	0.3
2	Dextran (70 kDa)	PIBCA – "brush-like" structure	0.8
3	Dextran sulfate (10 kDa)	PIBCA – "brush-like" structure	1.2
4	Dextran sulfate (40 kDa)	PIBCA – "brush-like" structure	1.9
5	Heparin (19 kDa)	PIBCA – "brush-like" structure	2.7

PIBCA=polyisobutylcyanoacrylate

As the data shows, everything else being equal, there is a nearly three fold difference in hemoglobin loading capacity between nanoparticles prepared by free radical mechanism (sequenced copolymer — "brush-like" structure) and nanoparticles prepared by the classical method (branched copolymer — "loop-like" structure) [1 and 2]. The polysaccharide molecular mass [3 and 4] as well as the nature of the polysaccharide [2 and 5] also affect the hemoglobin loading capacity. Finally, the presence of functional groups on the polysaccharide is also relevant [entry 2 with entries 3 and 4; and entries 2 and 5].

The claims are submitted to be patentable over the cited combination of art. Withdrawal of the Section 103 rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: /B. J. Sadoff/
B. J. Sadoff
Reg. No. 36,663

BJS:
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100